COMPUTATIONAL CANCER GENOMICS JUNIOR GROUP

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OVERVIEW

Cancer is a complex disease whereby cells grow and reproduce uncontrollably. One important feature necessary to understand cancer is its heterogeneity, which indicates that the effect of alterations could be different depending on the cellular context. In the Computational Cancer Genomics (CCG) Lab, we aim to understand the context-dependent cancer fitness landscape both by applying a computational approach and by setting up experimental collaborations. For example, we are specifically interested in changing the cancer fitness landscape depending on time, by analysing the associations between germline variants and somatic alterations, or by comparing the differences between the primary tumour and metastasis. In addition, we aim to further pursue how protein-protein interaction networks of cancer driver genes can be perturbed by their somatic or germline variants. We expect that our context-dependent cancer fitness landscape will provide a crucial direction for personalised medicine, since we are aiming to address the heterogeneity across patients, conditions, and cellular contexts.

"Through large-scale cancer genomics analysis, we aim to understand the complete cancer fitness landscape, analysing both germline variant- and somatic mutation-based perturbation of protein interaction."

RESEARCH HIGHLIGHTS

Context-specific genetic interaction perturbations

Metastasis is the main cause of death in cancer patients. However, most current cancer consortia have focused on primary cancer states. To gain a better understanding of the context-specific cancer fitness landscape across cancer statements, we systematically measured the association between somatic mutations and copy-number changes within the same genes across cancer types and compared their strengths of interaction between cancer statements. We found that several cancer types and cancer genes present significantly different preferences of interaction between mutations and copy-number changes and also proved that these differences are not due to medical treatments or genomic differences (*manuscript in preparation*). We expect that our findings will provide new insights to understand statement-specific perturbations and clues to develop better treatments for cancer patients.

Defining new cancer predisposition genes

Although large-scale cancer genomics data are rapidly accumulating, our understanding of cancer genes is highly biased towards somatic alterations and not germline variants. Germline frequencies are usually low, and there are several technical difficulties associated with their analysis. Since only 130 cancer predisposition genes (CPGs) are currently available, their contributions to cancer risk are underestimated. We hypothesised that germline variants in Mendelian-associated genes (OMIM genes) could contribute to increasing cancer risk. First, we proved that OMIM genes tend to have more pathogenic germline variants in cancer compared to controls (*manuscript under revision*). We then focused on a *PAH* that is associated with phenylketonuria, which presents the strongest enrichment in cancer compared to controls, and this enrichment is reproduced in other cancer data sets. Furthermore, through collaborations in South Korea, we addressed how metabolic dysfunction increases cancer risk experimentally, and we identified the possible contribution of OMIM genes as new CPGs. Currently, we are expanding this concept to predict novel CPGs, not only OMIM genes, by integrating multiple features using a machine learning approach. ■

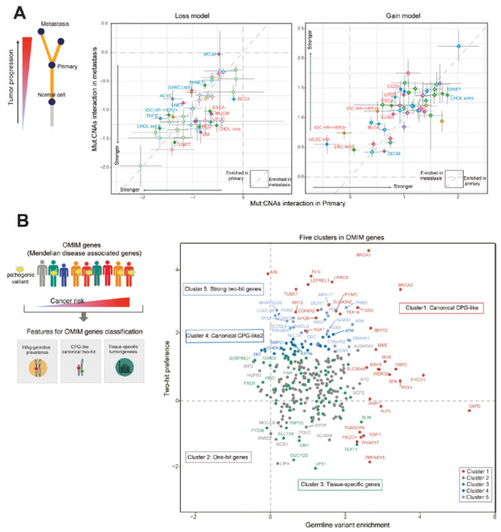

FIGURE 1 Understanding the cancer fitness landscape through both germline and somatic alterations. (**A**) Genetic interaction differences between primary tumours and metastases using 25,000 tumour samples. (**B**) Elucidating the role of Mendelian disease-associated genes as possible new cancer predisposition genes.